

Baseline dependence of the fMRI response: Elucidating the variable effects of induction agents

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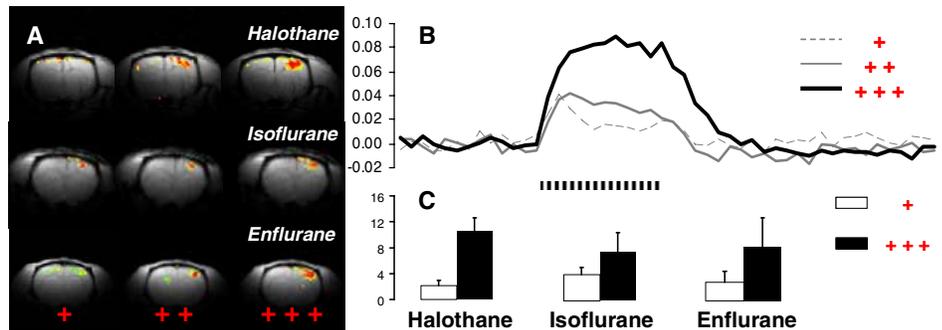
INTRODUCTION

Functional brain imaging in animals provide an essential platform for investigating mechanisms of neurovascular coupling, changes in metabolic activity, and the quantitative BOLD response [1-3]. Some degree of anesthesia is needed in functional activation studies to obviate pain associated with stimulation method and/or subject movement. While α -chloralose has become the popular anesthetic of choice for functional studies in rodents, prior to the treatment of this drug a variety of volatile agents (e.g., halothane, isoflurane, enflurane) are used during the surgical preparation phase of the experiment [4,5]. Since these volatile induction agents themselves may have some residual effects on the final anesthesia level reached with α -chloralose [6], it is important to know whether or not these effects modulate the functional response of the rodent to sensory stimuli. General anesthetics reduce neuronal activity in various regions of the mammalian CNS [7]. A considerable number of mechanisms have been suggested to mediate the depressant effects. However it is still a matter of debate as to which molecular targets are truly relevant in producing the "true" anesthetic state [4]. Recent studies reported the relationship between the action of volatile anesthetics occurring on the molecular level and the corresponding effects on neuronal firing [5]. Prior studies have also reported that volatile anesthetics depressed action potential firing of cells in the somatosensory cortex during sensory stimulation [6]. In this study we have used three volatile anesthetics (halothane, isoflurane and enflurane) and studied the time-dependent induction effects for functional studies in α -chloralose anesthetized rats.

MATERIALS and METHODS

Animal preparation: Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N₂O, 30% O₂). During the animal preparation halothane (1-2%), isoflurane (1-2%), or enflurane (1-2%) were used for induction. Intraperitoneal lines were inserted for administration of α -chloralose (46±4 mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO₂, pCO₂) throughout the experiment. The same forepaw stimulation paradigm (30 s block design; 2 mA; 0.3 ms; 3 Hz) was used for both fMRI and extracellular recordings. **fMRI measurements (n=10):** All fMRI data were obtained on a modified 9.4T Bruker horizontal-bore spectrometer (Billerica, MA) using a ¹H surface coil. The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15). **Extracellular (and laser Doppler) measurements (n=16):** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral and ipsilateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] were thinned and tungsten microelectrodes (FHC inc, Bowdoinham, ME) were inserted up to layer 4 with stereotaxic manipulators (Kopf). All signals were then digitized (>20 kHz) with a μ -1401 interface using SPIKE-2 software [3]. The data were first filtered to action and field potentials (AP, FP) and then the spiking data were examined for spike rates (ν) in 10 s bins. The CBF was measured using a bare fiber laser Doppler probe (Oxford Optronix, Oxford, UK).

Fig. 1



RESULTS and DISCUSSION

We examined the effects of halothane, isoflurane and enflurane used for induction in α -chloralose anesthetized rats. Electrical stimulation of the forepaw evoked BOLD signal changes in the contralateral somatosensory cortex (Fig. 1A). Graded increases in BOLD responses were observed with time as the α -chloralose anesthesia depth increased. An example of BOLD time courses under enflurane induction agent is shown in Fig. 1B. Earlier we had demonstrated changes in CBF were also time dependent under halothane and isoflurane induction agents [8]. In parallel we did electrophysiological measurements to study the change in neuronal activity under the above induction agents. We observed the correlation of neuronal spiking frequency with BOLD responses over time. A significant increase in neuronal spiking frequency was observed at ~5 hrs after the start of α -chloralose anesthesia for all the induction agents used (Fig. 1C). Initial reduction in BOLD and spiking response observed in first 2-3 hrs after transfer to α -chloralose anesthesia reflects the combined effects of induction agents and α -chloralose, as the former washes out with time.

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